JACC Vol. 21, No. 5
April 1993:1186–92

Implantable Cardioverter-Defibrillator Therapy in Survivors of Out-of-Hospital Sudden Cardiac Death Without Inducible Arrhythmias

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Objectives. The aim of this study was to determine the efficacy of implantable cardioverter-defibrillator (ICD) therapy in survivors of sudden cardiac death in whom no ventricular arrhythmias can be induced with programmed electrical stimulation.

Background. Survivors of sudden cardiac death in whom ventricular arrhythmias cannot be induced with programmed electrical stimulation remain at risk for recurrence of serious arrhythmias. Optimal protection to prevent sudden death in these patients is uncertain. This study compares survival in the subset of survivors of sudden cardiac death with that of patients treated with or without an ICD.

Methods. A retrospective study was performed on 194 consecutive survivors of primary sudden death who had ≤6 beats of ventricular tachycardia induced with programmed electrical stimulation with at least three extrastimuli. Ninety-nine patients received an ICD and 95 did not.

Results. There were no significant differences between the two groups in presenting rhythm, number of prior myocardial infarctions or use of antiarrhythmic agents. Patients treated with an ICD were younger (55 ± 16 vs. 59 ± 11 years, $p = 0.03$) and had a lesser incidence of coronary artery disease (48% vs. 63%, $p = 0.04$) and a lower ejection fraction (0.43 ± 0.16 vs. 0.48 ± 0.18, $p = 0.04$). There were no significant differences between the groups in the use of revascularization procedures or antiarrhythmic agents after the sudden cardiac death. Patients treated with an ICD had an improvement in sudden cardiac death–free survival ($p = 0.04$) but the overall survival rate did not differ from that of the patients not so treated ($p = 0.91$). A multivariate regression analysis that adjusted for the observed differences between the groups did not alter these results.

Conclusions. Survivors of sudden cardiac death in whom no arrhythmias could be induced with programmed electrical stimulation remained at risk for arrhythmia recurrence. Although the proportion of deaths attributed to arrhythmias was lower in the patients treated with an ICD, this therapy did not significantly improve overall survival.

(J Am Coll Cardiol 1993;21:1186–92)

Patients who are resuscitated from an episode of sudden cardiac death remain at risk for arrhythmia recurrence (1,2). Electrophysiologic studies have been used as a method to identify high risk patients. In patients with inducible arrhythmias, such studies can be used to guide drug therapy (3) and to identify patients who might benefit from surgical (4) or device (5) therapy. Patients without inducible arrhythmias remain at risk for recurrent sudden cardiac death with 2-year recurrence rates of 4% to 15% (6–11). In these patients, the findings of electrophysiologic studies cannot be used to guide therapy. Many physicians now use implantable cardioverter-defibrillators (ICDs) in this group in an attempt to prevent sudden death. Recent recommendations from the American College of Cardiology, American Heart Association and the North American Society of Pacing and Electrophysiology support this approach, although it has never been specifically evaluated in this patient group (12,13).

Because there have been no clear guidelines delineating the management of survivors of sudden death without inducible arrhythmias, patients have been treated with and without ICDs in our centers. The purpose of this study was to evaluate the efficacy of ICDs in this subgroup of survivors of sudden cardiac death and to determine those characteristics that might identify those patients who might benefit from their use.

Methods

Patients. In a retrospective study we evaluated 194 consecutive survivors of sudden cardiac death in whom no

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Manuscript received June 10, 1992; revised manuscript received October 5, 1992, accepted October 13, 1992.

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0735-1097/93/$6.00

arrhythmias could be induced on electrophysiologic study. Participating Northwest Electrophysiology Society centers included Oregon Health Sciences University (86 patients), the University of Washington (64 patients), Providence Medical Center, Seattle (28 patients), and Stanford University (16 patients). All patients who underwent electrophysiologic studies at our four centers between November 1980 and November 1991 were considered except those entered at Stanford where inclusion began in September 1984 because of a change in investigators. The following entry criteria were met by each patient: 1) survival after an out-of-hospital sudden cardiac death with sudden collapse and complete loss of consciousness requiring cardioversion to restore a stable rhythm; 2) no evidence of myocardial infarction within 14 days of the sudden cardiac death; 3) no significant underlying metabolic or electrolyte abnormalities and no history of alcohol or drug abuse or evidence of a proarrhythmic drug effect; 4) induction of ≤6 beats of ventricular arrhythmia on programmed electrical stimulation with at least three ventricular extrastimuli.

Programmed stimulation protocol. All antiarrhythmic drugs were discontinued for a period of at least 5 half-lives or until plasma concentrations were negligible before baseline electrophysiologic study. No patient had previously been treated with amiodarone. After each patient gave informed consent, multipolar recording and stimulation catheters were positioned in the right atrium, right ventricular apex and His bundle. Intracardiac and surface electrocardiographic (ECG) leads were recorded simultaneously. The protocol for all patients included a minimum of three extrastimuli from at least one ventricular site (two sites in 86%) and two basic drive cycle lengths (usually 600 and 400 ms) using a 2-ms rectangular pulse width at twice diastolic threshold.

Treatment. In all patients, efforts were made to optimize therapy of congestive heart failure and myocardial ischemia before electrophysiologic study. All patients underwent coronary angiography. Coronary artery bypass grafting or angioplasty procedures were performed before electrophysiologic study when clinically indicated (12% of patients).

After electrophysiologic evaluation, the use of beta-adrenergic blocking agents, the empiric use of class I antiarrhythmic agents or amiodarone and treatment with coronary artery bypass grafting or angioplasty procedures were determined by each patient's attending physicians. The use of ICD therapy was determined by recommendations of the attending physician, patient preference and the availability of devices.

Definitions. The following definitions are used. *Sudden cardiac death*: unexpected death within 1 h of the onset of symptoms. *Nonsudden cardiac death*: all other deaths judged to be from cardiac causes. *Noncardiac death*: all other deaths. *Appropriate ICD discharge*: a device discharge preceded by dizziness, presyncope or syncope or by ventricular tachycardia or ventricular fibrillation documented by ECG. *Inappropriate ICD discharge*: a device discharge that occurred during rhythms proved by ECG study to be other than ventricular tachycardia or fibrillation. *Asymptomatic ICD discharge*: a device discharge that occurred with no antecedent symptoms. *Arrhythmic events*: sudden cardiac death or an appropriate ICD discharge in the ICD-treated group; sudden cardiac death, aborted sudden death, syncope or sustained ventricular tachycardia in the patients treated without an ICD.

Follow-up. The majority of patients were followed up regularly by the investigators. Additional information was obtained by review of hospital and clinic records, autopsy reports and contact with referring physicians, the patients or their families. End points of follow-up were sudden cardiac death, nonsudden cardiac death and noncardiac death. Deaths were classified by two investigators (J.H.M. and P.J.K.) who had no knowledge of patient identity or the presence or absence of an ICD. They were given narrative descriptions of all available information on the patients' deaths. In 2 of the 31 deaths, these reviewers selected different death classifications, and in these cases the final classification was determined in blinded fashion by a third investigator (C.D.M.).

Statistical analysis. Standard deviation (mean ± SD) was used as the index of dispersion of observed values. Continuous variables were compared by using a *t* statistic and dichotomous variables with the chi-square statistic. A p value < 0.05 (two-tailed) was considered significant.

Actuarial curves for mortality and survival free of sudden cardiac death were constructed by using the Kaplan-Meier method (14) and compared with the Breslow-Gehan statistic (15). Length of follow-up was considered to be the time between the index event to the date of death or date the patient was last known to be alive. An intention-to-treat analysis was used and patients remained in their initial therapeutic group even if they crossed over to the alternate therapy. Survival is shown as the probability of survival ± SEE.

The effect of relevant covariates on recurrent arrhythmic events was evaluated using a Cox proportional hazards model. The effect of nine variables on the time to a recurrent arrhythmic event was tested: age (<60 vs. ≥60 years), gender, presence of remote myocardial infarction, presence of coronary artery disease, presenting arrhythmia (ventricular fibrillation or tachycardia or asystole) at the time of sudden cardiac death, left ventricular ejection fraction (<0.40 vs. ≥0.40), presence of a left ventricular aneurysm, use of beta-blockers after sudden cardiac death and use of revascularization procedures (coronary artery surgery or angioplasty, or both). After testing the univariate significance of individual variables in the Cox model, relations demonstrating important prediction of events ($p < 0.20$) were investigated further within the framework of stepwise multiple regression using the Cox proportional hazards model to examine their joint effects on outcome. Variables resulting in the best possible fit were included in the final model. The relative risk and 95% confidence interval associated with each variable in the final model, reflecting the

JACC Vol. 21, No. 5
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Table 1. Characteristics of the Study Group

	Patient Group		
	ICD (n = 99)	Non-ICD (n = 95)	p Value
Age (yr)	55 ± 16	59 ± 11	0.03
EF	43 ± 16	48 ± 18	0.04
CAD	48 (48)	60 (63)	0.04
Male	69 (69)	70 (76)	0.65
LV aneurysm	7 (7)	10 (11)	0.26
Prior MI	36 (36)	43 (46)	0.21
Prior use of class I antiarrhythmic agents	6 (6)	10 (11)	0.40
Presenting arrhythmia other than VF	7 (7)	13 (15)	0.21

Data are presented as mean value ± SD or number (%) of patient group. CAD = coronary artery disease; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LV = left ventricular; MI = myocardial infarction; VF = ventricular fibrillation.

relative contribution of the variable to the hazard of earlier arrhythmic events, were calculated after adjustment for the influence of the remaining variables in the model.

Results

Patient characteristics. Of the 194 patients who were evaluated, 99 received an ICD and 95 did not (Table 1). Patients receiving an ICD were significantly younger ($p = 0.03$), were less likely to have coronary artery disease ($p = 0.04$), and had a lower ejection fraction ($p = 0.04$) than did those who did not receive the device. There were no other significant differences between the groups (Table 1). There were no significant differences between the two groups in the use of class I antiarrhythmic agents, amiodarone or revascularization procedures after sudden death (Table 2). Follow-up was completed in 99% of patients in the ICD-treated group over a median of 22 months and in 97% of patients treated without an ICD over a median of 36 months.

Table 2. Treatment After Index Event

	Patient Group		
Therapy	ICD	Non-ICD	p Value
PTCA or CABG	27 (27)	29 (31)	NS
Beta-blockers	7 (7)	17 (18)	NS
Antiarrhythmic agents			
Class I	17 (17)	15 (16)	NS
IA	12 (12)	11 (12)	NS
IB	1 (1)	1 (1)	NS
IC	2 (2)	1 (1)	NS
Combination	4 (4)	5 (5)	NS
Class III	10 (10)	11 (12)	NS
None	70 (70)	60 (63)	NS

Data are presented as number (%) of patient group. CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

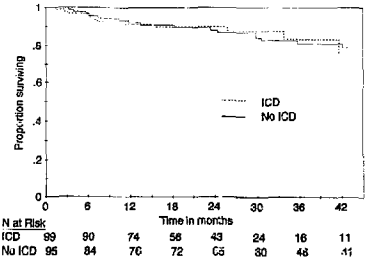

Figure 1. Overall survival comparing the groups treated with and without an implantable cardioverter-defibrillator (ICD) ($p = 0.95$). N = number of patients.

Survival. The overall survival rate was 0.88 ± 0.04 at 24 months for the ICD-treated patients and 0.90 ± 0.03 for the patients without an ICD (Fig. 1) with no significant differences in actuarial survival between the groups ($p = 0.95$). The 24-month sudden cardiac death–free survival rate was 0.97 ± 0.02 for the ICD-treated patients and 0.90 ± 0.03 for the patients without an ICD (Fig. 2). Over the entire follow-up period the ICD-treated patients were less likely to die of sudden cardiac death than were those without an ICD ($p = 0.05$). Over a median follow-up interval of 22 months, there were 12 deaths in the ICD-treated patients: 3 operative, 3 sudden cardiac, 4 nonsudden cardiac and 2 noncardiac. Over a median follow-up interval of 36 months there were 19 deaths in the patients without an ICD: 14 sudden cardiac, 4 nonsudden cardiac and 1 noncardiac.

Five of the patients in the ICD-treated group who died were being treated with antiarrhythmic agents (two with procainamide, two with quinidine and one with amiodarone).

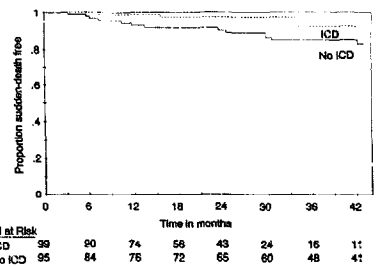

Figure 2. Sudden cardiac death–free survival comparing the groups treated with and without an implantable cardioverter-defibrillator ($p = 0.05$). Abbreviations as in Figure 1.

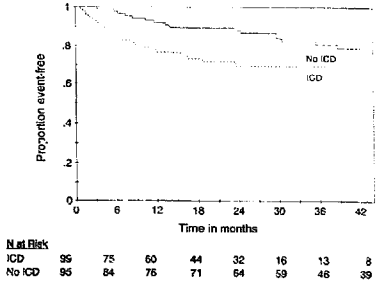

Figure 3. Arrhythmia event–free survival comparing the patients treated with and without an implantable cardioverter-defibrillator ($p = 0.004$). Abbreviations as in Figure 1.

Four of the deaths were nonsudden cardiac deaths and the patient being treated with quinidine died suddenly. Eight of the patients who did not receive an ICD died while receiving antiarrhythmic therapy (quinidine in three, procainamide in two, mexiletine in one and amiodarone in two); five of these eight patients died suddenly. The number of patients was too small to perform a meaningful statistical analysis to determine whether proarrhythmia may have caused some of these deaths.

Because of the observed baseline differences in age, ejection fraction and the prevalence of coronary artery disease, a Cox proportional hazards model of survival was used to adjust for these factors. There was no significant difference in survival between the groups with and without an ICD after this adjustment ($p = 0.91$). However, the ICD-treated patients had a significantly better sudden cardiac death–free survival rate ($p = 0.04$) after adjustment.

Arrhythmic event rates. The ICD-treated patients had a significantly higher arrhythmic event rate than that of the patients without an ICD ($p = 0.004$, Fig. 3). At 24 months the proportion event-free was 0.70 ± 0.05 for the ICD-treated group and 0.88 ± 0.04 for the group without an ICD.

The patients treated without an ICD had 20 arrhythmic events, of which 18 were fatal. The two nonfatal events consisted of syncopal ventricular tachycardia at 3 years in one patient and ventricular fibrillation at 6 months in the other. The first patient was treated with amiodarone and died 18 months later of congestive heart failure. The second patient received an ICD.

Of the 99 patients who received an ICD, 28 had arrhythmic events in follow-up: 3 events resulted in sudden death and 28 were accompanied by appropriate ICD discharges. All three patients who died suddenly had previously experienced appropriate ICD discharges. In addition, 8% of patients had documented inappropriate ICD discharges and 23% had asymptomatic ICD discharges.

Table 3. Predictors of Arrhythmic Events

Univariate Analysis	p Value
CAD	0.04
EF <0.40	0.001
Male	0.72
Age ≥60 yr	0.26
Prior MI	0.03
VT as presenting rhythm	0.13
LV aneurysm	0.42
PTCA or CABG after index event	0.64
Treatment with beta-blockers	0.66

Multivariate Analysis

Covariate	Regression Coefficient	95% CI	Relative Risk	95% CI
EF ≥0.40	−1.01	(−1.60 to −0.41)	0.36	(0.20 to 0.66)
CAD	0.45	(−1.09 to 0.16)	1.58	(0.34 to 1.02)

CI = confidence interval; VT = ventricular tachycardia; other abbreviations as in Tables 1 and 2.

Predictors of arrhythmic events. To determine preimplantation characteristics that predict recurrent arrhythmic events, univariate and multivariate analyses were performed (Table 3). In the univariate analysis, the presence of coronary artery disease, an ejection fraction <0.40 and the history of a prior myocardial infarction were significant predictors of recurrent arrhythmic events. In the multivariate analysis, only coronary artery disease and an ejection fraction <0.40 were predictive.

Subgroup analysis. Because left ventricular ejection fraction has been consistently demonstrated to correlate with outcome in survivors of sudden death (3,6,7), actuarial analysis was performed, stratified by ejection fractions (Table 4). In this analysis an ejection fraction cutoff value of 0.30 was used. When the ejection fraction was <0.30, the sudden cardiac death–free survival and overall survival rates were not significantly different between the patients treated with or without an ICD. In the patients with an ejection fraction ≥0.30, the ICD-treated patients had a higher sudden cardiac death–free survival rate ($p = 0.02$). Overall survival was not statistically significantly improved ($p = 0.44$) for the patients with an ICD.

Forty-one patients had no evidence of structural heart disease; 22 of these received an ICD and 19 did not. There were no deaths in either group. Five of the patients with an ICD had an appropriate device discharge.

Surgical complications. There were two initial operation-related deaths in the ICD-treated patients. Both patients had concomitant coronary bypass surgery, never regained consciousness after the operation and died of multisystem failure after a prolonged postoperative course (64 and 81 days, respectively). A third patient died of sepsis caused by a wound infection 17 days after battery replacement 26 months after the initial implantation.

Crossovers. Three patients in the ICD group crossed over to non-ICD treatment. In one patient, the ICD was removed

Table 4. Survival by Ejection Fraction < or ≥ 0.30

	EF <0.30		EF ≥0.30	
	ICD (n = 22)	Non-ICD (n = 17)	ICD (n = 73)	Non-ICD (n = 66)
Survival				
1 year	0.76 ± 0.10	0.75 ± 0.11	0.96 ± 0.02	0.95 ± 0.03
2 years	0.68 ± 0.11	0.75 ± 0.11	0.96 ± 0.02	0.90 ± 0.04
p value	0.37		0.44	
Sudden cardiac death-free survival				
1 year	0.94 ± 0.05	0.80 ± 0.10	1.0	0.95 ± 0.03
2 years	0.85 ± 0.10	0.80 ± 0.10	1.0	0.92 ± 0.04
p value	0.62		0.02	

p values are derived from the Mantel log-rank statistic comparing overall ICD and non-ICD group survival. Abbreviations as in Table 1.

because of a *Staphylococcus aureus* infection after 58 days and in another because of clinical evidence of constrictive pericarditis thought to be caused by the epicardial patches after 224 days. Both patients are still surviving. In the third patient adequate defibrillation thresholds could not be achieved and the ICD pulse generator was never placed. He was treated with amiodarone and is alive after 8 months of follow-up.

One patient was initially intended to be treated without an ICD but 6 months later, after a second episode of ventricular fibrillation, an ICD was placed. He is still surviving after 1 month of follow-up.

Discussion

The outcome in survivors of an out-of-hospital sudden cardiac death in whom ventricular tachyarrhythmias could not be induced with programmed electrical stimulation and who received an ICD was compared with that in a similar group of patients who were treated without an ICD. Both groups remained at risk for sudden cardiac death. Treatment with an ICD decreased the incidence of sudden death but did not change overall survival.

Survival. The 9% incidence rate of sudden cardiac death at 2 years in the patients without an ICD is consistent with reported rates of 4% to 15% in other recent trials (6–11). Only 2% of the ICD-treated patients in the present study had died suddenly at 2 years. This improvement in sudden cardiac death–free survival, presumably due to the ICD, is similar to that found in broader groups of patients with ventricular arrhythmias (5,15–21). However, the results of ICD therapy should be measured by its effect on survival. Kim et al. (22) and Guarnieri et al. (23) have demonstrated that sudden death rates alone overestimate the efficacy of these devices. They suggest that although ICD therapy may prevent sudden death, the operative mortality rate and nonsudden cardiac death rate may offset the gains made. In the present study, the surgical mortality rate was 3%, which is within the range of that of other published series (5,17). It may seem that this 3% rate would not have a significant impact on a group of this size. However, because event rates are low in this patient group, it constituted 25% of the deaths in the ICD-treated patients. These deaths in combination with those due to progressive congestive heart failure and other nonsudden cardiac deaths negated the improvement in sudden death survival.

Comparison with other studies. To our knowledge no previously published studies have evaluated the efficacy of ICDs in survivors of sudden cardiac death without inducible arrhythmias. However, there are several published studies (5,15–21) regarding the efficacy of these devices in broader groups of patients with ventricular arrhythmias. Three methods have been used to estimate the impact of ICDs on patient survival.

The first method is simply to report patient survival statistics without comparison with a concurrent control group. Winkle et al. (5) reported on their experience in 270 patients (5). The 1- and 3-year sudden death rates were 1% and 4% and total death rates were 8% and 18%, respectively. This study and others like it have been compared with historical series of medical and surgical therapy and these comparisons suggest a marked improvement in survival with ICD therapy (24). As with many new therapies, however, this method of comparison can be misleading because the patients studied may have been significantly different. Therefore caution must be used when using such data to make judgments about the overall impact on mortality.

The second method that has been used utilizes each patient as his own control. "Appropriate ICD discharges" are then used as an end point with the assumption that the patient would have died without the ICD in place. These studies have also suggested a dramatic improvement in survival with ICD therapy. Fogoros et al. (20) reported on their experience with 119 patients with severe underlying heart disease using this method. The actual survival rate was 85% compared with a projected survival rate of 31% at 3 years. Unfortunately, this method may also be unreliable. Currently approved ICDs do not have ECG monitoring capabilities and it is therefore difficult to determine which discharges were truly appropriate. Additionally, many

rhythms treated appropriately by the ICD may not have resulted in death. These limitations may lead to overestimation of ICD benefit.

The third method has compared a group of ICD recipients with a control group. Newman et al. (21) retrospectively compared 60 patients who presented with malignant ventricular arrhythmias and received an ICD with 120 patients matched for age, left ventricular ejection fraction, type of heart disease, type of presenting arrhythmia duration, and amiodarone response. The ICD-treated patients had an improved probability of survival ($p < 0.05$) with a 12-month survival rate of 0.89 compared with 0.72 in the control patients. The results cannot be directly compared with those of the present study because a different patient group was evaluated (most had ventricular arrhythmias induced with programmed stimulation).

Subgroup analysis. In the subgroup analysis we observed no improvement in survival due to an ICD in the patients with a low ejection fraction. Because patients with a low ejection fraction are at the greatest risk of sudden death recurrence (3,7), they would seem to be the most likely to benefit from an ICD. They didn't, probably in part because they had had the highest surgical mortality rate and incidence of nonsudden cardiac deaths. The sudden cardiac death–free survival was also not significantly improved in these patients with a low ejection fraction.

Among the patients with an ejection fraction ≥0.30, the ICD-treated patients had a higher survival rate at 2 years (0.96 vs. 0.90, p = NS). These patients have a lower risk of sudden death than do patients with worse left ventricular function but they also have a lower operative risk and lower risk of other cardiac mortality.

In the patients with no other evidence of heart disease there were no deaths in either therapy group. This outcome is consistent with another multicenter report suggesting that this is a low risk group (26). The presence of five patients in the ICD-treated group with "appropriate ICD discharges" again raises the question that the time to first shock method may overestimate the efficacy of these devices. An alternative explanation would be that the ICD-treated patients were selected appropriately, that they were higher risk patients and that they benefited from the shocks.

Limitations of the study. It is possible that selection biases may account for the lack of improvement in survival in the ICD-treated patients. Patients more likely to be at risk of recurrent sudden cardiac death may have received an ICD. Indeed one would expect that we would have attempted to place an ICD in those most likely to need one. However, the factors that drove these decisions were in most cases not based on such clinical variables. Forty-five percent of the patients who did not receive an ICD were treated before the device was available and 11% had had an ICD recommended but declined such therapy. Additionally other factors, including advanced age, high surgical risk and complex other medical problems, may have influenced avoidance of ICD use in sicker patients. There were slight differences in age, ejection fraction and the presence of coronary artery disease between the two groups; however, in regression modeling of survival, these factors did not affect the overall or sudden cardiac death–free survival comparison between patients in the ICD and non-ICD groups.

It is possible that other therapies such as treatment with angiotensin-converting enzyme inhibitors may have altered the results in these patients because these agents have been shown to improve survival in patients with heart failure (26). However, because more of the patients in the ICD group were treated during the period when angiotensin-converting enzyme inhibitors were routinely used, this group would have been more likely to benefit and it is therefore unlikely that such treatment would have masked a benefit of the ICD.

Despite attempts to determine differences between the two groups, we cannot exclude the possibility that a distinguishing variable was not analyzed. Only a prospective randomized trial would eliminate the possibility of this type of selection bias. However, such a trial in this group will require large numbers of patients and a long period of time to complete, given the low event rate and the relatively low numbers of noninducible sudden death survivors seen in any one center.

Clinical implications. Sudden cardiac death remains a major health problem, with an estimated 300,000 episodes/year in the United States (27). Implantable cardioverter-defibrillator therapy is a promising approach and surely has a role in treating many of these patients. As techniques become refined and newer generations of improved devices become available, the role of ICD therapy will continue to increase. If this therapy had low cost and little associated morbidity and mortality, it would be difficult to withhold from any patient at increased risk of sudden death. However, it remains an expensive step that is associated with significant morbidity and mortality. The present data suggest that ICD therapy prevents recurrence of sudden cardiac death but does not improve overall survival in the subgroup of survivors of the arrest in whom no arrhythmias can be induced with electrophysiologic study. We therefore recommend caution in applying this therapy to all such survivors until further information is available. Careful prospective trials will be needed to define the subgroups among these patients who will most benefit from the use of an ICD.

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